Early Screening for Gestational Diabetes Mellitus: A Systematic Review

by

Dana K Kelley

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Contents

Appendices

List of Tables

List of Figures

Abstract:

BACKGROUND: Gestational diabetes mellitus (GDM) is diabetes that is diagnosed for the first time during pregnancy. Rates of GDM in the U.S. and internationally have been rising in recent years. GDM is associated with an increased risk of adverse pregnancy outcomes, an increased risk of maternal Type 2 Diabetes Mellitus in the future, and an increased risk of future chronic disease for the neonate. Although recommendations differ, most guidelines recommend screening women with an oral glucose tolerance test during the second trimester of pregnancy and advise earlier screening in women considered high-risk for developing GDM.

AIMS: The objective of this systematic review will be to evaluate the accuracy of various methods of early screening for GDM as compared with traditional screening during the second trimester, and to determine whether earlier screening leads to improved maternal-fetal health outcomes.

METHODS: PubMed and the Cochrane Library were systematically searched according to pre-established eligibility criteria. Hand searches of relevant references and the grey literature were also done. One reviewer examined abstracts for eligibility and abstracted relevant data from included articles. Each included articles was assessed for quality.

RESULTS: Data on the accuracy and predictive ability of early screening was mixed. Early screening was done most often using fasting plasma glucose, however cutoff values that predicted gestational diabetes varied widely. Oral glucose tolerance testing and glycosylated hemoglobin were used infrequently as an early screening test. Though the data were also mixed on pregnancy outcomes associated with early screening, no outcomes were consistently shown to be improved through the process of early screening.

CONCLUSIONS: Due to heterogeneity of methods and inconsistent outcomes with early gestational diabetes screening, no method may conclusively be put forth as a superior method of screening for gestational diabetes early in pregnancy. Additionally, at this point, early screening overall cannot be justified due to a lack of evidence of improvement in maternal and neonatal outcomes. Future research should include better study designs, with more attention paid to clinically significant outcomes for women and their babies.

Introduction:

Defining Gestational Diabetes Mellitus: Physiologic changes to metabolism and the endocrine system take place during pregnancy to support the growth and development of the fetus. Resistance to insulin [similar to that seen in Type 2 Diabetes Mellitus (T2DM)] is often seen during the second and third trimesters of pregnancy. If the woman's pancreas is unable to compensate for this rising resistance by increasing the secretion of insulin, then blood glucose levels will begin to rise which may increase risk of adverse birth outcomes.[3] Increased risk of adverse maternal-fetal outcomes has been shown to have a linear relationship to elevated levels of plasma glucose. Therefore, any elevation in blood glucose levels above what is considered normal may increase a woman's risk of negative birth outcomes, whether or not the levels were high enough to qualify as GDM.[30] Gestational diabetes mellitus (GDM) is defined by the American Congress of Obstetricians and Gynecologists (ACOG) as glucose intolerance, which is recognized for the first time during pregnancy. This often includes both women who have previously undiagnosed T2DM as well as those who develop diabetes mellitus for the first time during pregnancy.[34] Most women diagnosed prior to 24 weeks of gestation are thought to have had pre-gestational T2DM. Approximately 6-8% of pregnancies in the United States are complicated by GDM, with an even higher rate in obese patients (up to 14%).[19] Internationally, rates of GDM are rising as well, closely paralleling the growing prevalence of mothers with advanced maternal age, obesity, and T2DM.[33]

Gestational Diabetes and Associated Risks: Pregnant women with GDM have been shown to experience increased risks of Cesarean delivery (odds ratio 1.88), stillbirth (odds ratio 2.00), and preeclampsia (odds ratio 1.61).[27] Resulting offspring are over three times more likely to be large for gestational age (LGA) and may be up to four times as likely to experience birth

injury, respiratory, cardiac and congenital disorders.[34] Women with GDM are also more likely to experience a shoulder dystocia during delivery (odds ratio 4.07).[20] Women who are diagnosed with GDM have a significantly increased risk of developing T2DM (odds ratio 3-7).[8, 18] Children born to mothers with GDM may have increased rates of obesity and T2DM in the future.[12]

Screening for Gestational Diabetes Mellitus: There are significant variations in screening guidelines as well as thresholds used to define GDM across international organizations. While recommendations differ between professional societies, most recommend universal screening of asymptomatic women between 24-28 weeks gestation, and earlier screening (before 20 weeks gestation) in high-risk women. Early screening is used in addition to second trimester screening and is hoped to lead to earlier identification and treatment of diabetes in pregnancy leading to better health outcomes. Risk factors for GDM include: advanced maternal age, increasing parity, ethnicity (e.g. Hispanic and African American populations), obesity, high gestational weight gain, physical inactivity, low-fiber high-glycemic-load diets, history of previous macrosomia or GDM, family history of T2DM, and history of polycystic ovarian syndrome (PCOS).[9, 26, 32] According to ACOG's 2001 guidelines, women with low risk of GDM may forego testing. This requires women to be under 25 years of age, not a member of a high risk ethnic group, BMI $\leq$ 25, have no history of abnormal glucose tolerance or macrosomia, and have no first-degree relatives with diabetes. However, only about 10% of pregnant women meet these criteria. Therefore, many physicians choose to screen all pregnant women.[1]

In the United States, the oral glucose tolerance test (OGTT) is considered to be the gold standard for diagnosis of gestational diabetes mellitus by ACOG and the United Stated Preventive Services Task Force (USPSTF). This tool has been shown to be more predictive of adverse pregnancy outcomes than other diabetes screening tools used in pregnancy, likely due to

the fact that GDM is primarily a post-prandial condition.[25] However, OGTT testing is expensive, unpleasant, and not well tolerated by some patients, especially those experiencing pregnancy related nausea.[3] Other organizations, such as the International Association of Diabetes in Pregnancy Study Group (IADPSG) and the American Diabetes Association (ADA) have recently begun to advocate for the use of Glycosylated Hemoglobin (HbA1c) levels for use in screening during pregnancy.[28] The IADPSG, ADA, and World Health Organization (WHO) recommend screening for diabetes at the first antenatal visit using an HbA1c value of $\geq 6.5\%$ as a diagnostic cut point,[22, 35] however this recommendation is based on data collected in non-pregnant patients. Some studies have shown that a reference interval of 4.3-5.4% should be used as normal values for A1C in pregnant women, while values between 5.7-6.4% are associated with impaired glucose tolerance and an increased risk (12-25%) of developing T2DM over the first ten years postpartum.[2, 21]

The most current recommendations by ACOG suggest using a two-step diagnostic approach with a 50-g, 1-hour OGTT between 24-28 weeks for screening, and follow-up testing using a 100-g, 3-hour diagnostic OGTT for all positive screens. Women with GDM are subsequently tested for continued diabetes at 6-12 weeks postpartum.[1] For many years the IADPSG has recommended a one-step approach to establishing a diagnosis. This includes a 75-g, 2-hour test done in the second trimester with a positive defined as any single threshold value met or exceeded (fasting value: 92 mg/dL; 1-hr: 180 mg/dL; or 2-hr: 153 mg/dL).[22] Some studies have demonstrated that, using IADPSG guidelines, universal screening using a 2-hour oral glucose tolerance test for GDM is marginally cost effective. Therefore, the cost of screening all women in the second trimester and treating those who test positive, is outweighed by the costs saved on complications associated with GDM (such as cesarean delivery, NICU admissions, etc.)

One study concluded that if cost of treatment for GDM is < $2630 and treatment is at least 74.9% effective at preventing complications associated with GDM, then the ICER was $61,503.[23] The ADA recommends screening for undiagnosed T2DM at first prenatal visit using a fasting value of 110-125mg/dL as a positive test, instead of > 92 mg/dL.[37] Increasingly since the early twentieth century, there has been a push toward international standardization of definitions and guidelines based on outcomes from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study.[12]

The HAPO study was a landmark study done in 2002 which aimed to set international diagnostic criteria for threshold values based on the predictive value for adverse pregnancy outcomes. This trial was done in approximately 25,000 women over five years and looked at birth outcomes such as cesarean delivery, increased fetal size (macrosomia/LGA/obesity), neonatal morbidity (hypoglycemia), and fetal hyperinsulinism. The study concluded that increased glycemic levels were related to increasing risk of adverse fetal outcomes. The IADPSG used the data from this study to create their recommendations for international screening guidelines.

Justification for a Systematic Review: Some organizations and practitioners have begun to investigate the utility of first trimester screening for GDM. The rationale behind this is that earlier detection and treatment of diabetes (either pre-gestational or gestational) may allow better glucose control throughout pregnancy, leading to better birth outcomes.[5] In order to justify implementing a new screening test, most experts recommend that an effective treatment must exist for patients identified through early screening, and there must be *evidence that this early treatment leads to better outcomes*.[29] Therefore, in order for researchers and clinicians to advocate for early GDM screening, there must be data supporting better health outcomes for

those women (and their children) who are screened at an earlier time period. This review will systematically search the recent literature to (1) understand the accuracy of early screening techniques and relevant threshold values among pregnant women, as contrasted to second trimester screening, in predicting or diagnosing pre-gestational or gestational diabetes mellitus, and (2) to explore the benefits and/or harms of first trimester screening versus second trimester screening and its relationship to birth outcomes (such as LGA, macrosomia, shoulder dystocia, and stillbirth).

Methods:

Two key questions (KQs) were posed for investigation by this review:

- KQ1. Are the available tests accurate in early pregnancy and what cutoff values should be used?
- KQ2. Does first trimester screening lead to better birth outcomes for mother and fetus than second trimester screening?

Search Strategy: No previous review protocol has been established for a review of these specific questions of interest. Therefore, methods for this review were formulated by the author using the PRISMA guidelines for performing and reporting systematic reviews. Databases searched include PubMed and the Cochrane Library from 2002 through June, 1 2016; the full search strategies are shown in Appendix 1. To identify unpublished (grey) literature, I also searched clinicaltrials.gov records and conducted hand-searches of key articles identified through database searches. The start date of 2002 was chosen for the database searches because another similar (but outdated), systematic review on screening for GDM was published at that time and

included literature searches through 2002.[29] That review concluded that evidence up to that point was limited and insufficient to justify early screening.

Inclusion/Exclusion Criteria: Inclusion and exclusion criteria of articles eligible for inclusion were broadly defined (***Table 1***). Study types included for analysis were randomized trials, previously published systematic reviews, and observational studies assessing the accuracy of first trimester screening compared to second trimester screening, or assessing the health benefits (maternal or child birth outcomes) resulting from earlier screening were included. The population of interest was pregnant women with no previous diagnosis of T1DM or T2DM. This includes studies investigating early screening in both low and high-risk populations. Articles were excluded if the study population was women with concurrent medical conditions (e.g. thyroid disease, Addison's disease, etc.) Studies were included from both developed and developing countries in order to assess and expand the external validity of the conclusions of this review. Due to the wide variety of current guidelines and criteria, studies were not excluded based on their definition of GDM. Studies were only included if the full text could be found in English. Additionally, articles were excluded if they did not contain original research (i.e. study protocols or responses to published articles) or did not investigate the interventions, controls, and outcomes of interest. Due to the limited amount of available literature on the established interventions and outcomes, the author felt that these broad eligibility criteria were appropriate in order to obtain a more inclusive understanding on the existing literature (*see* ***Table 1*** *for full inclusion and exclusion criteria*).

Table 1: Eligibility Criteria - full inclusion/exclusion criteria for studies in systematic review.

	Inclusion	Exclusion
Population	Pregnant women without a prior DM diagnosis (both low and high-risk populations), singleton pregnancies, and no concurrent medical conditions	Women with pre-gestational diabetes, multiple gestation pregnancies, concurrent medical conditions
Screening Intervention	Early glucose screening at or before 20 weeks gestation using any of the following methods: fasting plasma glucose, oral glucose tolerance testing, or HbA1C.	All other tests
Comparator	Second trimester screening between 24-28 weeks gestation by gold standard (oral glucose tolerance test)	All other comparators
Outcomes	KQ1: Diagnosis of GDM. KQ 2: Birth outcomes: preterm birth, C-section, LGA, shoulder dystocia, preeclampsia, macrosomia, stillbirth	All other outcomes
Timing of Literature Review	January 2002 to June 2016	Articles published before 2002
Outcome Timing	Participants identified in first trimester followed through birth	Participants did not present to provider or were not included in study in first trimester
Study Designs	Randomized controlled trials, observational cohort studies (retrospective and prospective), and systematic reviews	Non-systematic review, in-progress trials with no published results, case studies, case series
Language	Article available in English	Full article not available in English (only abstract available in English)

Study Selection: Articles identified by the database searches were exported into *RefWorks* for removal of duplicates. Those identified through ClinicalTrials.gov were assessed without exportation. A Microsoft Excel spreadsheet was used to track articles and for manual de-duplication of any duplicates missed by the *RefWorks* program. All abstracts were reviewed by one reviewer for their compatibility with the established inclusion and exclusion criteria. Full article PDFs were obtained for those articles deemed eligible by their abstracts for inclusion in this review. These full articles were subsequently assessed by the author for eligibility again based on inclusion and exclusion criteria. Those found to be relevant to one or both of the two key questions were included for final review (citations and reasons for exclusion are included in ***Figure 1***). Peer-reviewed publications and organizational and national guidelines were the preferred sources of data. Non-published and in-progress trials which did not have available results were excluded.

Synthesis of Evidence: Studies included in the final systematic review were critically appraised by one reviewer for risk of bias at the study level (i.e. selection bias, measurement bias, and confounding). Critical appraisal was done using the USPSTF Quality Rating Criteria (*See **Appendix 2** for USPSTF Quality Rating Criteria*). A narrative summary of articles meeting inclusion criteria was synthesized for a qualitative investigation of the status of current literature and recommendations.

Due to a limited number of heterogeneous studies meeting inclusion criteria and addressing one of the two KQs, no meta-analysis was performed. In addition to internal validity within included studies, external validity (i.e. applicability) of included studies was also assessed.

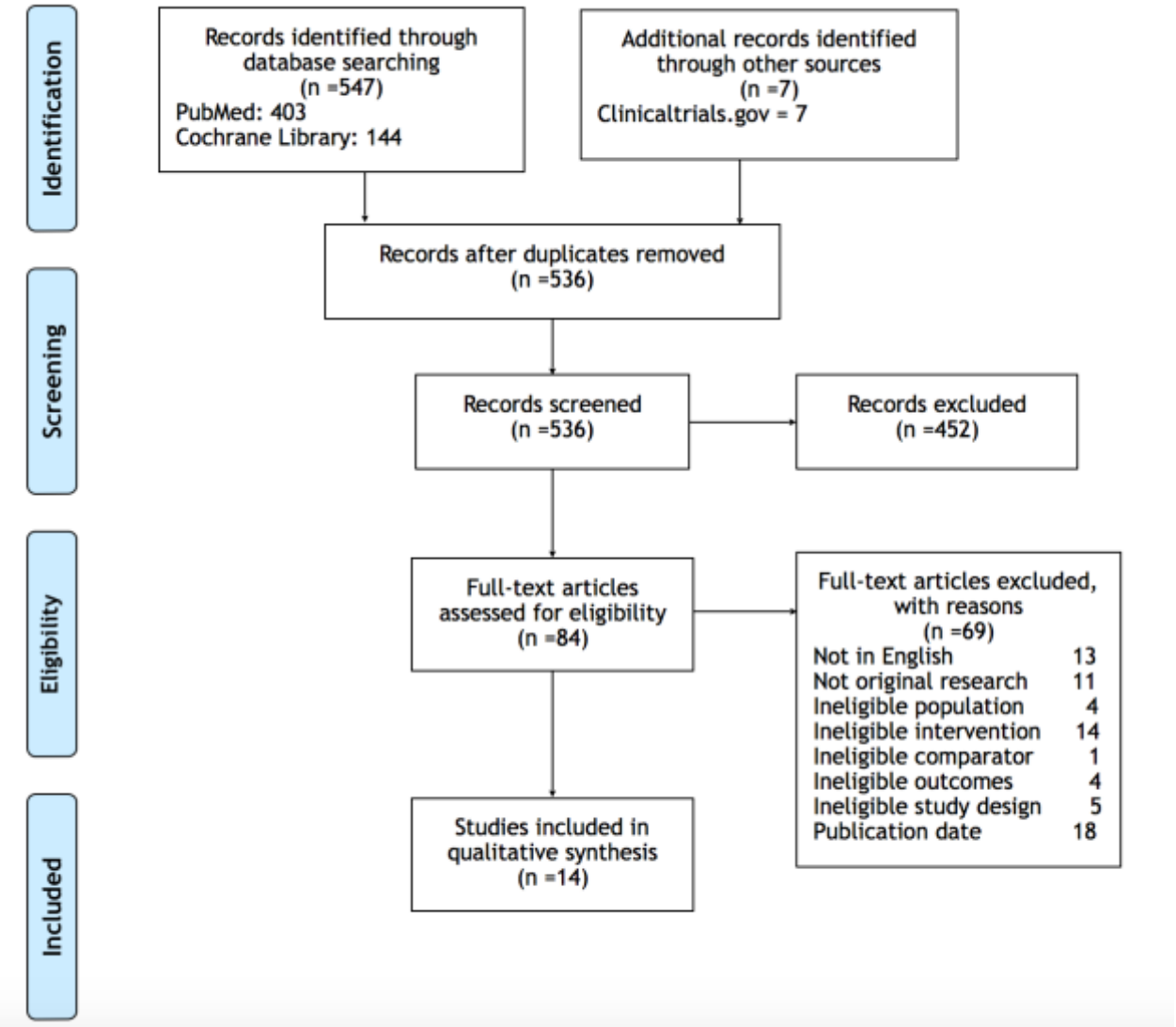

Figure 1. Article Flow Diagram.

Results:

Study Selection: Searches of PubMed, the Cochrane Library, and grey literature returned 536 search results, which were eligible for abstract screening. None of clinical trials.gov abstracts found had reported results, and therefore all of these trials (n = 7) were excluded. After

abstract review, 85 references underwent full-text review. Fourteen articles were included in the final evidence synthesis (*see* ***Figure 1*** *for full flow diagram of article inclusion and exclusion*).

Study Characteristics: Of these 14 studies, none were randomized controlled trials; two were systematic reviews and all others were cohort studies (both retrospective and prospective). The majority of studies were conducted in developed countries, however three were from developing countries (i.e. India, Pakistan, and China).[31, 34, 37]

Of the 14 included studies, nine addressed KQ1. Included strategies of first trimester screening were: fasting plasma glucose (6 studies), oral glucose tolerance tests (1 study), and glycosylated hemoglobin (2 studies). All studies enrolled women early in pregnancy prior to the time of traditional GDM screening (24-28 weeks gestation). Those women who tested within normal limits on the first screening test were then retested using OGTT between 24-28 weeks gestation as the gold standard. Of these nine studies, four were rated as good quality while the rest were judged to be of fair to poor quality.

Seven of the included studies examined birth outcomes in relation to early GDM screening and were therefore relevant to answering KQ2. The pregnancy outcomes most commonly reported across trials were preterm birth, preeclampsia, cesarean delivery, large for gestational age infant/macrosomia, shoulder dystocia, neonatal complications, and stillbirth. While some studies investigated only one of these outcomes (i.e. stillbirth)[34] each of these outcomes was addressed by multiple trials. The results and qualities of these studies varied widely. Three studies were rated as good quality, the rest were rated as fair to poor; common sources of bias across all studies included high risk of selection bias and no control for confounding factors (*see* ***Table 2*** *for study characteristics;* ***Table 5*** *for individual sources of bias by study*).

Table 2. Study characteristics of each study.

Study, Year	Study Design	Country	Sample Size	High risk vs random POI**	Study Period	Key Question
Alunni, 2015[4]	Retrospective cohort study	USA	1298	NR*	July 2010 - June 2012	KQ2
Bito, 2005[6]	Prospective observational study	Hungary	155	High Risk	Jan 1, 2001 - Sept 30, 2002	KQ1
Corrado, 2012[7]	Retrospective cohort study	Italy	738	Random	May 2010 - May 2011	KQ1
Fong, 2014[10]	Retrospective cohort study	USA	526	NR*	Jan 2011 - Jan 2013	KQ1; KQ2
Gandhi, 2011[11]	Retrospective cohort study	UK	190	High Risk	Jan 2009 - Feb 2011	KQ1
Harrison, 2015[13]	Prospective cohort study - as part of larger RCT	Australia	224	High Risk	2008-2010	KQ1
Hawkins, 2008[14]	Retrospective cohort study	USA	2257	High Risk	Dec 1999 - Jun 2005	KQ2

Hivert, 2012[15]	Retrospective cohort study	Canada	7839	High Risk	2004-2005; 2006-2007; 2008-2009	KQ2
Hughes, 2014[16]	Prospective cohort study	New Zealand	974	Random	2008-2010	KQ1; KQ2
Most, 2009[24]	Retrospective cohort study	USA	340	Random	2003-2007	KQ2
Scott, 2002[29]	Systematic review	UK	135 studies	High Risk	All literature through 2000	KQ1; KQ2
Seshiah, 2007[31]	Prospective cohort study	India	739	Random	NR	KQ1
Syed, 2011[34]	Systematic review	Study done in Pakistan; searched literature from all countries	70 articles included (14 intervention, 56 observational)	NR*	Literature up to 2010	KQ2
Zhu, 2013[37]	Retrospective cohort study	China	14039	Random	Jan 1, 2010 - Feb 29, 2012	KQ1

*NR: Not reported
**POI: Population of Interest

KQ1: Accuracy and Predictive Ability of First Trimester Screening

Three methods of early GDM screening were used across the included literature. First trimester fasting plasma glucose (FPG) was used most commonly (6 studies) with proposed threshold values ranging from 4.7 mmol/L to 5.6 mmol/L. One study supported the IADPSG threshold of ≥ 5.1 mmol/L, three studies that found evidence for lower threshold values, and only one study advocated for higher threshold values. One study investigated the accuracy of OGTT at the first antenatal visit. Lastly, two included studies evaluated the predictive ability of early hemoglobin A1c (HbA1c) screening (*See **Table 3** for a summary of studies addressing KQ1*).[10, 16]

First Trimester Fasting Plasma Glucose: Six of the included studies investigated the correlation between early FPG and later development of GDM. Women with overt diabetes (FPG values ≥7.0 mmol/L) at the first antenatal visit were excluded. Additionally, all studies used a 2-hour, 75-g OGTT as the gold standard of diagnosis of GDM between 24 and 28 weeks gestation. However, not all studies defined GDM using the same threshold values (WHO, IADPSG, Australasian Diabetes in Pregnancy Society [ADIPS], etc.).

FPG = 5.1 mmol/L: Two articles supported a threshold value similar to that proposed by the IADPSG (5.1 mmol/L). Using an FPG cutoff value of ≥ 5.1 mmol/L, Corrado et al. found an adjusted OR (aOR) of 7.1 (95% CI:3.8-13.1) when compared to FPG values < 5.1 mmol/L, and an area under the receiver operating characteristic (ROC) curve of 0.614 (95% CI: 0.544-0.684).[7]

FPG < 5.1 mmol/L: Three studies examined threshold values < 5.1 mmol/L. Similar to IADPSG guidelines Bito et al., posit a cutoff value for FPG at ≤ 16 weeks gestation of ≥ 5.0 mmol/L.[6] This threshold value was associated with an aOR of 3.8 (95% CI: 1.1-13.4) of developing GDM at 24-28 gestational weeks. Additionally, this value had a negative predictive

value (NPV) of 0.92 of being diagnosed with GDM at 24-28 weeks gestation. One study enrolling obese women (BMI ≥ 40) concluded that an FPG of ≥ 4.7 mmol/L was an optimal cutoff point in this population.[11] However, this study found that this value had a low sensitivity 78.5% (95% CI:48.8%-94.2%) and specificity 43.7% (95% CI: 35.5%-52.2%). The positive liklihood ratio (LR) was only 1.39 (95% CI: 1.02-1.90) and the area under the ROC curve was unremarkable at 0.56 (95% CI: 0.39-0.72). A study by Harrison et al., enrolled high risk women as identified by a risk prediction tool, which included previous GDM, family history, high risk ethnicity, age, and BMI.[13] This investigation looked at the ability of early FPG to predict GDM development as defined by both IADPSG and ADIPS criteria. Elevated FPG was defined in this study as ≥ 4.91 mmol/L (> 6.7 mmol/L was judged to be diagnostic of pre-gestational diabetes). This threshold value had an aOR of 6.32 (95% CI: 2.49-16.06) for predicting GDM diagnosed using ADIPS criteria, with a sensitivity of 34.0% and a specificity of 94.8%. In predicting GDM diagnosed by IADPSG criteria, this value had an aOR of 10.03 (95%CI: 3.40-29.56) with a sensitivity of 50.0% and a specificity of 92.4%. The area under the ROC curve was 0.79 (95% CI: 0.72-0.86) for ADIPS criteria and 0.83 (95% CI: 0.77-0.90) for IADPSG criteria.

FPG > 5.1 mmol/L: Only one study investigated a higher cutoff value than that proposed by IADPSG.[37] Median first trimester FPG was found to be 4.58 ± 0.44 mmol/L across all women. Incidence of GDM diagnosis was strongly correlated with increase in FPG (chi-square = 959.3, $p < 0.001$). The incidence of GDM development was 52.7% in women with a first trimester FPG between 5.6-6.09 mmol/L. The area under the ROC curve was calculated to be 0.654 (95% CI: 0.643-0.665; SE 0.006; $p < 0.001$).

Results of Systematic Reviews: A systematic review done in 2002 concluded that higher diagnostic threshold values should be used due to the finding that risks to the mother and fetus

increase linearly with increasing FPG values.[29] Therefore, lower values equal lower risk, and in order for the benefits of screening to outweigh the costs and harms, higher threshold values must be used. Additionally, this study concluded that FPG values < 4.8 mmol/L may be used to exclude the subsequent development of GDM. This review also conceded that, although FPG may be an attractive screening method, data have shown that fetal weight gain may be more closely linked with postprandial glucose values.[17] Because FPG does not test postprandial values, and because some women who have normal FPG levels may have elevated postprandial levels, Scott et al. conclude that FPG may not be the most relevant screening test for GDM and associated birth outcomes.

Oral Glucose Tolerance Testing: Only one study investigated the relationship between early oral glucose tolerance testing and the subsequent development of gestational diabetes.[31] This study used 2-hr, 75-g OGTT at the first antenatal visit irrespective of gestational week (mean gestational age of these women at first antenatal visit was *23.55* weeks). A threshold value of ≥ 140 mg/dL was used as diagnostic of GDM according to the WHO criteria. A cohort of women who screened negative at their first prenatal visit, but who were subsequently diagnosed with GDM later in pregnancy (mean gestational age 30 weeks) were retrospectively divided into OGTT values < or ≥ 120 mg/dL at first antenatal screen. Of these women, 56% (who went on to develop GDM) had first visit OGTT levels < 120 mg/dL and 44% had values ≥ 120 mg/dL. The authors concluded that regardless of 2-hr OGTT results at the first antenatal visit, all women who test negative for GDM at this time should be rescreened at subsequent visits.

Glycosylated Hemoglobin: The remaining two studies addressing KQ1 investigated Hemoglobin A1c (HbA1c) values as predictors of GDM development. The IADPSG does not give a threshold value for GDM diagnosis using HbA1c. They propose that physicians use a

value of ≥ 6.5% to diagnosis overt diabetes in pregnancy. These women were excluded in both studies.

The first of these studies included women who received a HbA1c test at ≤ 20 gestational weeks.[10] Those women who had a first trimester HbA1c value between 5.7-6.4% had an aOR of 2.38 (95% CI: 1.01-5.63) for developing GDM when compared with their counterparts who had HbA1c values < 5.7%. The second study, found that the optimal HbA1c threshold value to diagnose GDM was ≥ 5.9%.[16] In this study women were asked to have a 2-hr, 75-g OGTT at < 20 weeks gestation, and the HbA1c value of ≥ 5.9% was correlated with those women who had a positive OGTT test. This HbA1c value was 98.4% specific (95% CI: 97.0-99.9) but only 18.8% (95% CI 6.6–31.1) sensitive for detection of early GDM. The area under the ROC curve for HbA1c and GDM correlation was 0.711.

Table 3. Summary Table of Results for KQ1

Study/Year	Screening Test (Threshold)	Gestational Age	Comparator	Outcomes	Results
Corrado, 2012[7]	FPG (≥ 5.1 mmol/L)	First trimester	2-hr, 75-g OGTT, 24-28w	GDM diagnosis	FPG ≥ 5.1 mmol/L: aOR = 7.1
Bito, 2005[6]	FPG (≥ 5.0 mmol/L)	≤ 16w	2-hr, 75-g OGTT, 24-28w	GDM development	FPG ≥ 5.0 mmol/L: aOR = 3.8
Gandhi, 2011[11]	FPG (≥ 4.7 mmol/L)	20w	2-hr, 75-g OGTT, 28w	GDM at 28w	FPG ≥ 4.7 optimal cutoff for GDM prediction at 20w

Harrison, 2015[13]	FPG (4.91-6.70 mmol/L)	≤ 15w	2-hr, 75-g OGTT, 26-28w	GDM development by ADIPS and IADPSG criteria	aOR = 6.32 predicting ADIPS GDM; aOR = 10.03 predicting IADPSG GDM
Zhu, 2013[37]	FPG (≥ 5.6 mmol/L)	First prenatal visit (median 13.4w)	2-hr, 75-g OGTT, 24-28w	GDM development	FPG ≥ 5.6 mmol/L: 99% specificity
Scott, 2002[29]	FPG (< 4.8 mmol/L)	< 24w	OGTT, 24-28w	GDM development	FPG < 4.8 mmol/L: excludes GDM
Seshiah, 2007[31]	OGTT (≥ 120 mg/dL)	First prenatal visit (median 23.6w)	2-hr, 75-g OGTT at subsequent visits (median 30w)	GDM development	Of women who developed GDM, 56% had early OGTT ≥ 120 mg/dL, 44% had early OGTT < 120 mg/dL
Fong, 2014[10]	HbA1c (≥ 5.7%)	≤ 20w	One or two step OGTT at 24-28w	GDM development	HbA1c ≥ 5.7%: aOR = 2.38
Hughes, 2014[16]	HbA1c (≥ 5.9%)	< 20w	One or two step OGTT at 24-28w	GDM development	HbA1c ≥ 5.9%: 100% sens, 97.4% spec; HbA1c < 4.8%: excludes GDM

FPG: Fasting plasma glucose
HbA1c: hemoglobin A1c (glycosylated hemoglobin)
OGTT: Oral glucose tolerance test

KQ2: Early screening and pregnancy outcomes

The second interest of this review is to determine if early screening for gestational diabetes mellitus leads to better birth outcomes for the mother and the neonate. Only two studies showed any benefit for early screening. And this was seen only in selected outcomes. The majority of maternal and fetal outcomes were not different in women who were screened early than in those who were screened later. Two studies actually reported worse maternal and fetal outcomes in women who were identified through early screening than those identified in the second trimester (*see **Table 4** for a summary of articles addressing KQ2*).

Macrosomia and Large for Gestational Age: Of the seven studies addressing KQ2, four found similar birthweights and rates of LGA and macrosomic infants born to mothers screened for GDM early versus those screened in the second trimester. Hivert et al. found similar birthweights (kg) (early = 3.360 [3.080-3.690], traditional = 3.380 [3.040-3.650]) and rates of macrosomia between those who received early screening and traditional screening.[15] Hawkins et al. found similar rates of LGA and macrocosmic infants in both early and traditional cohorts after adjusting for maternal age, race, parity, weight, and glycemic control.[14] Another study found no differences in neonatal outcomes between women screened before 20 weeks gestation and women screened at or after 20 weeks gestation.[10] A similar study from 2015 found similar birthweights and rates of macrosomia in infants born to mothers screened before or after 24 weeks gestation.[4]

A study from 2009 found that rates of LGA (18% vs. 6% [P=0.02]) and macrosomia (14% vs. 6% [P=0.001]) were twice as high (1.8% vs 4.4%) among infants born to mothers identified through first trimester screening.[24] Although the data seem to suggest that early screening does not decrease the rates of LGA and macrocosmic infants, the 2002 systematic

review by Scott et al. concluded that the utility of early screening should not be decided based on rates of macrosomia.[29] These authors argue that macrosomia is an intermediate outcomes and not a relevant clinical outcome. The utility of early screening must be evaluated by looking at reduction of harmful health outcomes.

Cesarean Delivery: Four studies investigated rates of cesarean delivery associated with timing of screening. Two of these studies[4,10] found that rates of C-section did not change between mothers screened earlier, and those screened in the second trimester. Most et al. found rates of cesarean delivery to be 45% in the early diagnosis group and 24% in the late diagnosis group (P=0.002),[24] and Hawkins et al. found a non-statistically significant increase in the odds ratio of repeat cesarean delivery among this group.[14] Taken together the data suggest that earlier screening may not reduce rates of cesarean delivery and may actually increase rates when compared to traditional diagnostic measures.

Gestational Age and Preterm Birth: The data found a similar story regarding rates of preterm birth and gestational age at delivery. Alunni et al. and Hivert et al. found an average gestational age at delivery of 39 weeks in both early screening and late screening cohorts.[4, 15] Two studies found increased risk of preterm birth in the early screening population. Most et al. did not find a statistically significant difference between groups, however 6.1% of the early cohort in comparison with 5.4% of the late cohort were born preterm (P=0.79).[24] Hawkins et al. attributed this to higher rates of preeclampsia (aOR=2.4 [95% CI:1.5-3.8]) leading to early delivery.[14]

Preeclampsia: Only three studies investigated preeclampsia as a maternal outcome as it relates to GDM screening. Two found maternal outcomes such as preeclampsia were worse for women identified through early screening.[14, 24] Most et al. found a non-significant increase in

hypertension among mothers identified earlier (19.4%) compared to mother identified later (12.4%; P=0.10). The last study found no difference in rates of maternal preeclampsia between early and traditional cohorts.[4]

Shoulder Dystocia: Only two studies addressed shoulder dystocia as an outcome of interest and these studies found opposing results. One study by Hawkins et al. concluded that women with diet-treated GDM who were identified before 24 weeks had lower rates of cesarean deliveries for dystocia (3%) than women with diet-controlled diabetes mellitus identified at or later than 24 weeks gestation (6%; p = 0.02).[14] In direct contrast to that data, the study by Most et al. found increased rates of shoulder dystocia in the early screening cohort leading to a mixed picture surrounding shoulder dystocia.[24]

NICU Admission and Stillbirth: Of three studies which looked at rates of NICU admissions and/or stillbirth, one found that early screening in the setting of a specialized diabetes clinic led to decreased rates of neonatal intensive care unit (NICU) admissions (15.4%) compared to second trimester screening (20.8%; P=0.002).[15] Two papers found similar rates of neonatal complications between the two cohorts (including NICU admission and intrauterine fetal demise [IUFD or stillbirth]). A systematic review done of the literature published prior to 2010 concluded that it was not possible to show that early testing was superior to later testing in improving rates of stillbirth.[34] This review found only one study and one review article investigating the relationship between early GDM screening and IUFD. This review also concluded that threshold values or guidelines used to screen for and diagnose GDM (ADA vs. WHO) had no bearing on stillbirth rates. This conclusion was based on data from two observational studies.

Outcomes and First Trimester HbA1c: One study was identified that compared first trimester hemoglobin A1c value (HbA1c) with perinatal outcomes.[16] This study proposed an early HbA1c threshold value of 5.9%. In women with elevated first trimester HbA1c, risk of preterm birth was elevated with an aOR of 1.66 (95% CI: 1.01-2.74), as well as risk of shoulder dystocia (aOR=2.48 [95% CI:1.21-5.10]) and preeclampsia (aOR=3.04 [95% CI: 1.97-4.70]). Risk of perinatal death was also found to be higher in this population though the odds ratio was not significant after adjusting for confounders (aOR=2.24 [95% CI: 0.75-6.69]).

Table 4. Summary Table of Results for KQ2

Study/Year	Screening Test (Threshold)	Gestational Age	Comparator	Outcomes	Results*
Hawkins, 2008[14]	RPG (≥ 130 mg/dL)	< 24w	Two step OGTT at 24-28 weeks	Preeclampsia, repeat cesarean, SHD, LGA, macrosomia	Decreased cesarean for dystocia in early group; no difference in LGA or macrosomia; increased preeclampsia and cesarean
Hivert, 2012[15]	1-hr GCT (≥ 10.3 mmol/L)	First trimester (0-13w)	GCT in the second trimester	Duration of gestation, cesarean, neonatal comp, NICU, bwt, macro	Decreased NICU in early group; no difference in duration of gestation, cesarean, neonatal comp bwt, macro; increased
Fong, 2014[10]	HbA1c (≥ 5.7%)	≤ 20w	One or two step OGTT at 24-28w	Cesarean, NICU, bwt, macro, IUFD	All outcomes equal in both groups

Alunni, 2015[4]	HbA1c (≥ 5.7%) or FPG (≥ 92 mg/dL)	≤ 24w	2-hr, 75-g OGTT at 24-28 weeks	Maternal and neonatal outcomes, delivery mode, gestational age at delivery	All outcomes equal in both groups
Syed, 2011[34]	Not specified	First trimester	Regular screening (24-28w)	Stillbirth	No difference in stillbirth
Most, 2009[24]	50-g GCT (≥ 140 mg/dL) and 100-g OGTT	First trimester	OGTT at 24-28 weeks	Macro, LGA, cesarean, preterm, SHD, preeclampsia	Increased rates of all outcomes in early group
Hughes, 2014[16]	HbA1c (≥ 5.9%)	< 20w	One or two step OGTT at 24-28w	Preeclampsia, SHD, stillbirth, preterm	HbA1c ≥ 5.9%: increased rates of all outcomes

*Results: Results report increase, decrease, or no change in magnitude of effect (not necessarily statistically significant)
GCT: Glucose Challenge Test
Bwt: birthweight
Macro: Macrosomia
Neonatal comp: neonatal complications
NICU: neonatal ICU admission
Preterm: Preterm birth
SHD: Shoulder dystocia

Discussion:

Interpretation of the Evidence: The risk of bias of each individual study was assessed, and internal and external validity was assessed (*see **Table 4** for risk of bias within each study*). The data supporting the accuracy of early screening for gestational diabetes are mixed. The majority of the data to date have investigated fasting plasma glucose prior to 20 weeks gestation as the optimal test for early GDM screening. Fewer studies have used oral glucose tolerance

testing or glycosylated hemoglobin, but both of these methods are also of interest for use during early pregnancy.

Current international guidelines recommend using a fasting plasma glucose value of ≥ 5.1 mmol/L as a threshold value for diagnosing GDM. Studies have shown that FPG values change throughout pregnancy, and this review found evidence supporting threshold values from 4.7 mmol/L to 6.1 mmol/L as optimal cutoff values for early GDM screening. One systematic review proposed that a value of < 4.8 mmol/L could be used to rule out the future development of gestational diabetes mellitus at early screening.

Oral glucose tolerance testing has also been investigated and suggested cutoff values range from ≥ 140 mg/dL to ≥ 153 mg/dL for early diagnosis of GDM. Additionally, values < 140 mg/dL have not been found to be sensitive for ruling out GDM development later in pregnancy, and women who screen negative at their first antenatal visit should be screened again during the second trimester regardless of the results of their first OGTT. Fewer guidelines exist regarding the use of HbA1c as a diagnostic test in pregnancy. This is partially attributable to the fact that most data on optimal HbA1c thresholds come from studies done in non-pregnant populations. The studies investigating HbA1c values suggest using a cutoff between 5.7-5.9% as predictive of GDM development in pregnancy.

Although various threshold and cutoff values for early screening and diagnosis of GDM have been posited by different national and international organizations, the available literature has yet to support a common value in all situations. This is likely due, in part, to the fact that rates of and risk factors for gestational diabetes vary by ethnicity, by region, by setting, by lifestyle, and by genetics. Therefore, it is possible that the present search for an international consensus on guidelines is not feasible. The literature has also demonstrated consistently that

there is a linear relationship between blood glucose in pregnancy and the associated negative outcomes. This suggests that any amount of elevation in blood glucose levels during pregnancy increases a woman's risk of developing harmful outcomes and should therefore be considered abnormal. However, it also suggests that any level chosen as a threshold will necessarily be somewhat arbitrary.

In accordance with KQ2, additionally, none of these methods of early screening for, or detection of, GDM have been consistently linked to better pregnancy outcomes. The large majority of studies included found no differences in pregnancy or birth outcomes for those women who received early screening when compared to those women who received standard, second trimester screening. Infrequently, single outcomes in various studies were found to improve among the group who received earlier screening, but these findings were not reproducable in other studies.

Furthermore, women who were diagnosed with GDM earlier in pregnancy were often found to have higher rates of pregnancy complications than those diagnosed later. This is likely due to the study design of these studies. Instead of using two cohorts of women, one who received earlier screening, and one who received later screening, all of these studies used the same cohort of women. These women received early screening, and then those who tested negative early in pregnancy were screened again in the second trimester. Therefore, rather than measuring the effects of early screening on outcomes, these studies were actually measuring early onset versus later onset development of GDM. This means that those who were diagnosed earlier in pregnancy likely had more severe cases of GDM and fetuses were exposed to elevated blood glucose levels for a longer period of time, likely leading to the conclusion that earlier

screening and diagnosis leads to worse outcomes. In the future studies should screen different cohorts of women in the first and second trimesters to avoid this confounding effect.

A potential source of confounding across studies was that not all studies defined 'early screening' the same. All included studies performed screening prior to the traditional 24 weeks gestation, but in some cases it was limited to screening before 15 or 16 weeks, and the median values for gestational age of women who received early screening varied widely between the studies. This could cause results to vary based on when early screening was performed and GDM was identified. The tests used to perform early screening in the studies on KQ2 varied widely between studies. This might cause variability in results between studies. However, despite this potential source of confounding, these studies overwhelmingly found similar results (i.e. no difference between early and late screening). This increases our confidence in the conclusions of this review. Furthermore, many different sets of criteria were used across the body of literature. While this should not have affected numerical values and cutoff points, it may have affected outcomes associated with 'early identification' if that definition changed across studies.

Some experts have expressed concern that fasting plasma glucose may be suboptimal to investigate fetal and maternal outcomes in relation to gestational diabetes. This is because postprandial glucose levels have been implicated in macrosomia and adverse pregnancy outcomes. FPG does not take postprandial glucose levels into account and may result in false negatives, when the fetus is actually being exposed to higher than normal levels of glucose in utero. Therefore, hemoglobin A1c was judged by the author to be the ideal method for first trimester screening. This is to limit the number of women who have to undergo oral glucose tolerance testing and to capture a more comprehensive picture of glucose levels (both fasting and postprandial) which may lead to negative pregnancy outcomes.

Table 5. Risk of Bias by Individual Study

Study	Potential for selection bias (+ to +++) and explain	Potential for measurement bias (+ to +++)	Potential for confounding (+ to +++)	Overall judgment of internal validity (good, fair, poor)	External validity: applicability to other populations
Alunni, 2015[4]	++ Initial comparability: Early screen group - fewer RFs; Dropouts: None	++/+++ Equal: Cohorts from different times; Valid: Phamacotx as surrogate marker; Reliable: Good	++ Adjusted for BMI as only confounder	**Fair**	Maternal and neonatal implications unknown. Applicable to US populations but unsure about international
Bito, 2005[6]	++/+++ Initial comparability: NR; Dropouts: None	++ Equal: NR; Valid: WHO criteria; Reliable: Good	++/+++ NR	**Fair/Poor** Lack of transparenc y.	Unsure about applicability across races. No assessment of lifestyle differences
Corrado, 2012[7]	++/+++ Initial comparability: Fair; Dropouts: Small number (due to inadequate data)	++ Equal: Many labs ran tests; Valid: IADPSG criteria; Reliable: Good	+/++ Adjusted for maternal age and pre-pregnancy BMI	**Fair**	Caucasian population - difficult to extrapolate to other races and other healthcare settings

Fong, 2014[10]	++ Initial comparability: Interest group with more risk factors; Dropouts: None	++ Equal: Two screening methods; Valid: Early A1c not validated; Reliable: Good	+ Adjusted for age, race/ethnicity, pre-pregnancy BMI, gestational age at HbA1C sample collection, gestational age at GDM screening/diagnosis, and method of GDM screening (2-step vs. 1-step)	**Good**	Primarily Hispanic population with a high prevalence of obesity - may not apply to different demographics
Gandhi, 2011[11]	++/+++ Initial comparability: Good; Dropouts: large number excluded due to failure to have tests at 20 and 28 weeks.	+ Equal: Good; Valid: Good; Reliable: Good	+++ Not adjusted for significant confounders	**Fair**	Obese, Caucasian population. Limited information on GDM risk factors.
Harrison, 2015[13]	++ Initial comparability: Good; Dropouts: Some lost to follow-up	+ Equal: Good; Valid: Good; Reliable: Good	+ Adjusted for age, baseline BMI, ethnicity, previous GDM and family history of T2DM	**Good/Fair**	High risk population may not be generalizable. Tool not validated in BMI < 25. Ethnically diverse study population

Hawkins, 2008[14]	++/+++ Initial comparability: Early screening only in high-risk; Dropouts: More early screen likely to be ineligible	++ Equal: Good; Valid: National Diabetes Data Group criteria; Reliable: Good	+/++ Adjusted for demographics and lifestyle/glycemic control	**Fair**	Largely Hispanic population. Screening guidelines different in different countries
Hivert, 2012[15]	+/++ Initial comparability: Groups from different settings; Dropouts: None	++ Equal: Cohorts from different times/settings; Valid: Good; Reliable: Good	+++ Unable to adjust for pre-pregnancy BMI and family history	**Fair**	Specialty clinic may be increase interaction with health care providers or more intense monitoring
Hughes, 2014[16]	++/+++ Initial comparability: higher risk factors in higher BMI group; Dropouts: High	+ Equal: Good; Valid: Good; Reliable: Good	+++ Outcome frequencies too low to adjust for potential confounders	**Fair**	Primarily low-risk Caucasian population
Most, 2009[24]	++ Initial comparability: Fair; Dropouts: NR	+/++ Equal: Good; Valid: Dependent on criteria; Reliable: Good	+/++ Adjusted for maternal age. ethnicity, BMI, parity, previous cesarean delivery	**Good/Fair**	Inner city, largely Hispanic and Asian populations
Scott, 2002[29]	+ Multiple reviewers	++ Equal: Non-transparent measurement; Valid: Good; Reliable: Good	++ NR	**Good/Fair**	International guidelines. Good

Seshiah, 2007[31]	++ Initial comparability: Few demographic collected; Dropouts: NR	++/+++ Equal: Cohorts from different times Valid: WHO criteria Reliable: Good	+++ Not adjusted for age/BMI	**Poor**	Done in India, few demographics reported. Difficult to extrapolate.
Syed, 2011[34]	+ Multiple reviewers	+ Equal: Re-ran all calculations; Valid: Meta-Analysis; Reliable: Good	++ NR	**Good**	Developing and developed countries. Good
Zhu, 2013[37]	++ Initial comparability: Fair; Dropouts: None	++ Equal: Good; Valid: Chinese MOH criteria Reliable: Good	++ Adjusted for age and different testing locations. Did not adjust for BMI	**Good/Fair**	Chinese population and guidelines used.

NR: Not reported

Limitations: There were several limitations associated with the available body of evidence. The most significant limitation identified was a lack of randomized controlled trials. This is possibly due to a prevailing hesitancy to randomize pregnant women to interventions that may be harmful or have not been shown to improve outcomes for women and their babies. Additionally, many of the established guidelines and criteria are based off of data collected in non-pregnant populations and may not be applicable or appropriate criteria to apply to screening pregnant women.

The limitations of this review are twofold. The review was performed by a single reviewer, increasing the risk of bias of study selection and quality ratings. Additionally, only two databases were searched, and only articles published in English were able to be included due to

constraints on time and personnel. It is likely that articles exist in other journals and languages that investigated out questions of interest but were not included.

Future Directions: Due to the lack of evidence supporting better outcomes in those women who receive earlier screening and interventions, randomized controlled trials to investigate the accuracy and utility of first trimester GDM screening would be ethically justifiable. RCTs are needed both that establish accuracy of the available tests and the best thresholds, as well as studies that investigate maternal and neonatal outcomes of early screening versus standard screening.

Secondly, the gold standard oral glucose tolerance test is an unpleasant tool that is not well tolerated by many pregnant women. Therefore, in addition to searching for highly specific first trimester tests which predict or diagnose GDM, there would be high clinical utility in the discovery of a highly sensitive test or threshold value that could rule out GDM development. This test would allow women with very low risk to forgo the second trimester OGTT and its associated burdens, as well as decreasing rates of false positives.

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Conflict of Interest:

The author has no conflicts of interest to disclose.

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Appendix A. PubMed Search Strategy: the following search strategy was used for the PubMed database:

("diabetes, gestational"[MeSH Terms] OR ("diabetes"[All Fields] AND "gestational"[All Fields]) OR "gestational diabetes"[All Fields] OR ("gestational"[All Fields] AND "diabetes"[All Fields])) AND ("pregnancy outcome"[MeSH Terms] OR ("pregnancy"[All Fields] AND "outcome"[All Fields]) OR "pregnancy outcome"[All Fields]) AND ("mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields]). Searches results were filtered to include only studies done since 2002 and studies done in humans.

Appendix B. USPSTF Quality Rating Criteria. Adapted from PubMed Health. Accessed at http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0009125/ on 6 June 2016.

Initial comparability of groups	RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
Maintenance of comparable groups	Includes attrition, cross-overs, adherence, contamination
Loss to follow-up	Important differential loss to follow-up or overall high loss to follow-up
Measurements	Equal, reliable, and valid (includes masking of outcome assessment)
Interventions	Clear definition of interventions
Outcomes	Important outcomes considered

Analysis	Adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs (i.e. analysis in which all participants in a trial are analyzed according to the intervention to which they were allocated, regardless of whether or not they completed the intervention)

Appendix C. Data Extraction Tables - by Study

Study 1 **KQ1**	Alunni, M. L., Roeder, H. A., Moore, T. R., et al. (2015) *First trimester gestational diabetes screening- change in incidence and pharmacotherapy need*
Study Question:	How do GDM diagnosis rates compare using the standard two-step approach versus early screening and secondarily how do pharmacotherapy needs and perinatal outcomes compare?
Source of Funding:	NR
Source Population:	Two cohorts from the California Diabetes and Pregnancy Program at UCSD. Total UCSD prenatal population
Study Population:	Singleton pregnancies diagnosed between 7/2010 and 6/2012. Two cohorts identified by review of clinic dataset and electronic chart review. Excluded: pts with multiple gestations, pre-pregnancy T1DM or incidental dx of T2DM (A1C $\geq$ 6.5% or FPG $\geq$ 126 in first trimester.
Design:	Retrospective cohort study
Intervention:	Women diagnosed early (HbA1C $\geq$ 5.7% or FPG $\geq$ 92mg/dL at $\leq$ 24 weeks)
Intervention Setting:	UCSD Diabetes and Pregnancy Program (DAPP)
Comparison:	Women diagnosed at 24-28 weeks (2-hr OGTT)

Measurement:	No info on total number screened - so no data on rates of dx. Maternal age, parity, BMI, and ethnicity were abstracted from EMR. Maternal outcomes: mode of delivery and gestational age at delivery. Neonatal birth weight and length (for ponderal index). Early diagnosis cohort analyzed to calculate proportions of pts dx with GDM via A1C, FPG, and OGTT to determine pharmacotherapy as well as gestational age at initiation of pharmacotx. No info on those who screened negative therefore no predictive values of screening.
Results:	BMI strongest predictor of need for pharmacotherapy. But method of dx remained significant. At an HbA1C of 5.7%-5.9% over half of pts required pharmacotx. Over 70% of those diagnosed with FPG elevations needed meds. Maternal and neonatal outcomes of mode of delivery and gestational age at delivery were similar for all groups. Neonatal outcomes of weight and ponderal index did not differ
Attrition:	No dropouts, retrospective data collection. No data on those who screened negative
Quality Score:	Fair

Study 2 **KQ1**	Bito, T., Nyari, T., Kovacs, L., & Pal, A. (2005). *Oral glucose tolerance testing at gestational weeks ≤ 16 could predict or exclude subsequent gestational diabetes mellitus during the current pregnancy in high risk group*
Study Question:	What OGTT cut-off values at gestational age ≤ 16 weeks can predict or exclude subsequent onset of GDM in a high risk group?
Source of Funding:	Not reported
Source Population:	163 pregnant women at high risk of gestational diabetes.

Study Population:	155 women who had not had prior GDM or altered carbohydrate metabolism in a previous pregnancy, but who had one or more risk factors and were enrolled at ≤ 16 weeks gestation. Family history of T2DM, history of large neonate, history of adverse perinatal outcome, obesity, and age were all risk factors. Included women were not opposed to any medication or dietary restriction. Eight patients were excluded from the further analysis as GDM was diagnosed by this first OGTT at gw ≤ 16.
Design:	Prospective observational study
Intervention:	2-hr 75-g OGTT at ≤ 16 weeks and FPG
Intervention Setting:	Women referred to a special Diabetic Pregnant Outpatient Department in Hungary
Comparison:	2-hr 75-g OGTT at 24-28 weeks; 2-hr 75-g OGTT at 32-34 weeks
Measurement:	2-hr 75-g OGTT and FPG. Patients were considered to have GDM in the event of a glucose level of ≥ 7.0mmol/L fasting or ≥ 7.8 mmol/L at 120 min according the WHO criteria. Incidence of family history of T2DM, history of large neonate, adverse perinatal outcome, obesity and age and glycosuria were all recorded (unclear if used medical records or patient self-report)
Results:	54% of high-risk women developed GDM. 4.9% at ≤ 16 gw; 19.6% at 24-28 gw; 29.4 % at 32-34 gw. Best cut-off value for fasting glucose was ≥ 5 mmol/l: OR=3.8 (1.1-13.4) for developing GDM at 24-28 weeks. No correlated risk at 32-34 weeks. Best post load level 6.2: OR = 7.5 (1.0-57.8) at 24-28 wks and OR = 2.6 (1.1-6.5) at 32-34 wks. Combined 5.3 and 6.8 with obesity is strongest predictive factor for GDM at 32-34 weeks. OR = 6.0 (1.7-21.0)
Attrition:	No loss to follow-up
Quality Score:	Poor/Fair

Study 3 **KQ1**	Corrado, F., D'Anna, R., Cannata, M. L., et al. (2012). *Correspondence between first-trimester fasting glycaemia and oral glucose tolerance test in gestational diabetes diagnosis.*

Study Question:	What is the correspondence between first-trimester fasting glycaemia and the results of the OGTT in diagnosing gestational diabetes?
Source of Funding:	Not reported
Source Population:	775 consecutive Caucasian pregnant women scheduled for OGTT early in 3rd trimester
Study Population:	738 eligible patients. Exclusions due to twin pregnancy, no first trimester FPG assay, or FPG diagnostic of pre-gestational diabetes
Design:	Retrospective cohort study
Intervention:	First trimester fasting plasma glucose
Intervention Setting:	Department of Obstetrics and Gynecology, University of Messina, Italy
Comparison:	2-hr 75-g OGTT at 24-28 weeks according to the IADPSG guidelines
Measurement:	2-hr 75-g OGTT according to the IADPSG Consensus Panel Criteria. Women were asked to provide first trimester FPG results (not all done at same lab). If this value was < 7.0 mmol/l they underwent OGTT and were evaluated according to IADPSG criterial. Lab was blinded to and pre-existing values of FPG. At end of trial period women's charts were reviewed and correspondence between the two different diagnostic strategies compared.
Results:	11.9% of eligible patients diagnosed with GDM according to ADA. When ≥ 5.1 mmol/L was used as a cutoff for first trimester screening crude OR = 8.0 (4.4-14.6) and adjusted OR = 7.1 (3.8-13.1)
Attrition:	18 did not have first trimester FPG and 6 had FPG value after first trimester. One excluded b/c first trimester FPG diagnostic of diabetes
Quality Score:	Fair

Study 4 **KQ1**	Fong, A., Serra, A. E., Gabby, L., et al. (2014). *Use of hemoglobin A1c as an early predictor of gestational diabetes mellitus*
Study Question:	Can an early HbA1C value of 5.7-6.4% be used as an early predictor of progression to GDM?
Source of Funding:	NR
Source Population:	All women who delivered at a single institution over 2 years who had an early screening HbA1C test performed at ≤ 20 weeks of gestation.
Study Population:	526 women met inclusion criteria. Women were included if they had a screening HbA1C test at ≤ 20 0/7 weeks of gestation and had been delivered by our practice from Jan 2011 to Jan 2013. Women with known preexisting diabetes mellitus or HbA1C values ≥ 6.5% were excluded. Or if they did not undergo screening or did not deliver at the institution
Design:	Retrospective cohort study
Intervention:	HbA1c at ≤ 20 weeks gestation
Intervention Setting:	MemorialCare Center for Women at Miller Children's Hospital in Long Beach, CA
Comparison:	1 step (2-hr, 75-g) or 2 step (1-hr, 50-g & 3-hr, 100-g) OGTT at 24-28 weeks gestation
Measurement:	Two different screening methods included, may increase ROB. Primary outcomes: GDM development. Secondary outcomes: delivery route, maternal weight gain, birthweight, and neonatal morbidities (NICU admission, neonatal hypoglycemia, hyperbilirubinemia, transient tachypnea, or acute respiratory distress) (5-minute Apgar score < 7, birthweight, macrosomia, SGA, fetal demise). Blinding not discussed.

Results:	Women with HbA1c levels 5.7-6.4% had 2.4 fold higher odds of the development of GDM when compared with HbA1c < 5.7% counterparts. No statistically significant difference b/w groups on who needed medical treatment. No difference in C-section or weight gain. Mean 1-hr OGTT significantly higher in 5.7-6.4 group as was fasting glucose. Neonatal outcomes - no difference in composite adverse neonatal outcomes (NICU admission, hypoglycemia, hyperbilirubinemia, transient tachypnea, or acute respiratory distress), low Apgar, birthweight, macrosomia, SGA, IUFD. Subgroup analyses: A1c ≤ 14 0/7 weeks to evaluate 1st trimester. Significantly more in the 5.7-6.4 group developed GDM. Second subgroup, obese women (prepregnancy). In obese pts - those in the 5.7-6.4 group more significantly more likely to develop GDM. In non-obese, no significant difference.
Attrition:	None
Quality Score:	Good

Study 5 **KQ1**	Gandhi, P., & Farrell, T. (2011) *Gestational diabetes mellitus (GDM) screening in morbidly obese pregnant women.*
Study Question:	What are the outcomes of two-stage GDM screening of morbidly obese women, and what is the diagnostic performance of 20-week OGTT values in predicting or excluding late onset GDM?
Source of Funding:	No external sources of funding
Source Population:	295 pregnant women with BMI ≥ 40 who delivered in the center
Study Population:	190 women with BMI ≥ 40. Women who followed the GDM screening protocol. Exclusion: women with pre-existing diabetes mellitus, previous gestational diabetes and who failed to attend OGTT at either 20 or 28 weeks were excluded
Design:	Retrospective cohort study
Intervention:	2-hr, 75-g OGTT at 20 weeks and fasting plasma glucose

Intervention Setting:	High BMI clinic at the Royal Hallamshire Hospital, Sheffield, UK
Comparison:	75-g OGTT at 28 weeks gestation
Measurement:	All samples measured at the same site and the machine calibrated yearly for quality assurance. All women measured at same gestational age
Results:	Glucose ≥ 6mmol/L was the optimal cutoff value for the 2-h OGTT to predict GDM at 28 weeks. Fasting glucose ≥ 4.7 was optimal cutoff for fasting glucose levels at 20 weeks OGTT. Positive likelihood ratio 2.19 and negative likelihood ratio of 0.12.
Attrition:	105 women excluded: 39 had normal OGTT at 20 weeks but did not follow-up at 28 weeks. 20 had first OGTT test at 28 weeks. 38 did not have the test either at 20 or 28 weeks.
Quality Score:	Fair

Study 6 **KQ1**	Harrison, C. L., Lombard, C. B., East, C., et al. (2015). *Risk stratification in early pregnancy for women at increased risk of gestational diabetes.*
Study Question:	Can fasting glucose and lipids be added to a simple, validated risk prediction tool for GDM applied in early pregnancy?
Source of Funding:	BRIDGES grant from the International Diabetes Federation (supported by an education grant from Lilly Diabetes). And the Jack Brockhoff Foundation
Source Population:	Women at risk of developing GDM on a validated risk prediction tool (developed using retrospective cohort in 2008)
Study Population:	Recruitment at three large tertiary teaching hospitals in metropolitan Melbourne (2008-2010). Invited to participate by invitation letter if ≤ 15 weeks gestation, had singleton pregnancy, were overweight or obese, and at increased risk of GDM on risk prediction tool. Exclusion criteria: diagnosed T1DM or T2DM, non-English speaking, pre-existing chronic medical condition.

Design:	Prospective cohort study - as part of a larger randomized controlled trial
Intervention:	Early pregnancy fasting plasma glucose
Intervention Setting:	Three large tertiary teaching hospitals in metropolitan Melbourne, Australia
Comparison:	2-hr, 75-g OGTT at 26-28 weeks gestation
Measurement:	This is one part of a larger study which investigated the addition of biochemical measures to a previously validated risk prediction tool. Focus on impact of fasting blood glucose and lipid measurement taken in early pregnancy on GDM risk prediction. All outcomes measures were completed at baseline (12-15 weeks) and 26-28 weeks. Basic demographic data collected at baseline. Venous blood sampling for biochemical markers. At 26-28 weeks women did 1 step OGTT to assess for GDM. All data pooled and stratified according to GDM outcome.
Results:	Baseline characteristics did not vary between GDM and non-GDM groups. Fasting glucose and triglycerides were higher in the GDM groups diagnosed using both ADIPS and IADPSG. For IADPSG GDM women they had higher proportion of previous GDM and higher age. Those with higher baseline plasma glucose had significantly higher weight, fat mass, and lower HDL in early pregnancy and higher OGTT later in pregnancy than those with lower plasma glucose in early pregnancy. Elevated fasting triglyceride and glues predicted ADIPS GDM (adjusted and unadjusted). Elevated fasting triglycerides, glucose, and low HDL predicted IADPSG GDM. Fasting glucose strongest predictor for both groups
Attrition:	10% misdirected to have (Australian) standard 50-g glucose challenge test and did not progress to OGTT
Quality Score:	Fair/Good

Study 7 **KQ1**	Hawkins, J. S., Lo, J. Y., Casey B. M., et al. (2008). *Diet-treated gestational diabetes mellitus: Comparison of early vs routine diagnosis*
Study Question:	How do pregnancy outcomes compare in women with diet treated GDM diagnosed at < 24 weeks to those diagnosed at ≥ 24 weeks.

Source of Funding:	NR
Source Population:	87,057 women delivered between 1999 and 2005
Study Population:	2257 women with diet treated GDM screening for GDM between 24-28 weeks unless they had glucosuria, random serum glucose ≥ 130 mg/dL, history of GDM, or symptoms such as polydipsia or polyuria (these women were screened immediately). Women who were identified to have diet treated GDM, singleton pregnancy, and cephalic fetuses without major fetal malformations. Excluded: non-cephalic infants, and insulin treated diabetes
Design:	Retrospective cohort study
Intervention:	Women with diet-treated GDM that was diagnosed at < 24 weeks
Intervention Setting:	Parkland Hospital
Comparison:	Women with diet-treated GDM that was diagnosed at ≥ 24 weeks
Measurement:	All women received screening between 24-28 weeks unless showed risk factors. Then were given two step OGTT and diagnosed based on National Diabetes Data Group thresholds. If negative, women were tested again at 24-28 weeks. Pregnancy outcomes entered into a computer operations database. Antepartum info entered into separate database and linked electronically to pregnancy outcome data. LGA and shoulder dystocia
Results:	Women with early dx more likely to be older, multip, and obese. Women with early diagnosis had significantly higher mean results for the 50-g OGTT. Early dx had higher mean fasting glucose but also greater decrease in fasting glucose throughout pregnancy. Women with early dx had higher rates of preeclampsia leading to early gestational age at delivery, higher rate of repeat cesarean deliveries but fewer for dystocia. Infants more likely to be LGA and hyperbili. LGA did not persist when adjusted for demographic characteristics and weight
Attrition:	398 of those diagnosed before 24 weeks were treated with insulin and therefore ineligible. 679 of those diagnosed after 24 weeks treated w/ insulin
Quality Score:	Fair

Study 8 **KQ1**	Hivert, M. F., Allard, C., Menard, J., et al. (2012) *Impact of the creation of a specialized clinic for prenatal blood sampling and follow-up care in pregnant women*
Study Question:	What is the effect on gestational diabetes mellitus screening rates of having a specialized clinic for pregnant women offering blood sampling and screening for GDM and what is the impact on perinatal outcome of having early GDM screening and follow-up provided by the specialized clinic?
Source of Funding:	Canadian Diabetes Association, Fonds de la recherche en santé du Québec, and the Canadian Institutes for Health
Source Population:	Women who delivered during a period when the BSP clinic was operating compared to those before the clinic was established. Women who had GDM screening in the first trimester with women who had screening during the second trimester and with women not screened
Study Population:	2468 deliveries during the 2004-2005 period, 2591 from 2006-2007 and 2780 from 2008-2009.
Design:	Retrospective cohort study
Intervention:	Specialized diabetes clinic, GDM screening in the first trimester (median = 9.9 gw [8.3-11.6])
Intervention Setting:	Regional hospital
Comparison:	Women screened in the second trimester (median 27.0 gw [25.9-27.7]) and women not screened.
Measurement:	Diagnosis of GDM based on diagnostic codes in the summary discharge forms admitted for delivery. Clinical data available in electronic health records (results of testing not always included - only diagnosis). Different time frames may reflect differences in clinical practices outside of BSP clinic and early testing. Tried to control for this by comparing two time frames before the opening of the clinic. Historical control groups

Results:	C-section rate increased over time but held stable after the clinic was established. No significant difference in duration of gestation, birth weight, macrosomia, and rates of fracture/dislocation between three periods. Maternal age and duration of gestation similar for early vs late vs no screening. GDM more often diagnosed in women screened during 1st trimester. C-section higher in women who did not have GCT during pregnancy than those who had early screening. Offspring more likely to have complications if no screening than first trimester screen. Babies less likely to be admitted to NICU if early vs late screening and no screening. Median birth weight and macrosomia similar in three subgroups
Attrition:	NR
Quality Score:	Fair

Study 9 **KQ1**	Hughes, R. C., Moore, M. P., Gullam, J. E., et al. (2014). *An early pregnancy HbA1c>/=5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes*
Study Question:	What is the optimal HbA1c threshold for detecting diabetes in early pregnancy as defined by an early OGTT at < 20 weeks and what pregnancy outcomes are related to this threshold?
Source of Funding:	Canterbury Medical Research Foundation, the New Zealand Society for the Study of Diabetes, the New Zealand National Lottery Grants Board, the Health Research Council of New Zealand, and the Diabetes Research and Training Trust of Christchurch, New Zealand
Source Population:	16,122 women in Christchurch NZ between 2008-2010.
Study Population:	Subset of women who got a HbA1c measurement with their first antenatal bloods and completed an early OGTT. 4021 women invited for OGTT, 974 had OGTT before 20 weeks. Exclusion criteria: known preexisting diabetes, multiple gestation, pregnancy loss.
Design:	Prospective cohort study

Intervention:	HbA1c at first antenatal blood draw; subset had early OGTT
Intervention Setting:	Primary care setting in Christchurch, New Zealand
Comparison:	2-hr, 75-g OGTT or 50-g & 75-g OGTT at 24-28 weeks gestation
Measurement:	HbA1c measure at median 47 days. Used A1c ≥ 5.9% and < 6.5%. 75-g 2-h OGTT performed before 20 weeks. WHO criteria applied retrospectively to define diabetes and GDM. Research assistants collecting data were blinded to both the HbA1c and OGTT results. Three labs involved in blood sampling - techs blinded to HbA1c. All labs used identical methods. Possible variation calculated at 0.02%. OGTT subject to preanalytical error d/t variation in sample handling and having reproducibility issues. HbA1c measurements more reproducible.
Results:	HbA1c cutoff ≥ 5.9%: 100% sens, 97.4% spec, 18.8% PPV. HbA1c < 4.8% excluded early GDM. Women with A1c ≥ 5.9% compared with women with A1c < 5.9% had a greater than 2-fold increase RR of preeclampsia, shoulder dystocia, and major congenital anomaly; greater than 3-fold increase RR of perinatal death; greater than 1.5-fold increased RR of delivery before 37 weeks gestation. Higher risk of adverse pregnancy outcomes persisted even when those treated for GDM were included (except fetal death).
Attrition:	3047 women invited to have OGTT did not complete
Quality Score:	Fair

Study 10 **KQ1**	Most, O. L., Kim, J. H., Arslan, A. A., (2009). *Maternal and neonatal outcomes in early glucose tolerance testing in an obstetric population in new you city.*
Study Question:	How do pregnancy outcomes compare in women who were diagnosed with GDM early in pregnancy with those diagnosed at the standard 24-28 weeks gestation?
Source of Funding:	NR

Source Population:	340 pregnant women evaluated
Study Population:	340 women with GDM, in a singleton pregnancy coming from an inner city population in NY, NY from 2003 to 2007.
Design:	Retrospective cohort design
Intervention:	Women diagnosed early in pregnancy
Intervention Setting:	Inner city hospital
Comparison:	Women diagnosed at the standard 24-28 weeks.
Measurement:	All patients screened with GCT at first pregnant visit. Positive screen + OGTT $\geq$ 2 abnormal values diagnosed GDM. Normal results underwent testing at 24-28 weeks. Maternal and neonatal data obtained from computerized diabetic database: maternal age. ethnicity, BMI, parity, previous cesarean, gestational age at dx, and lab results from GCT/GTT. Maternal and neonatal outcomes (mode of delivery, gestational age at birth, metal birth wt, Apgars, preterm delivery, hypertensive disorders, shoulder dystocia, lacerations).
Results:	Early onset GDM: higher BMI, older, higher parity, no difference in race, more pharmacotx. Macrosomia and LGA higher in early GTT groups. Cesarean higher in early group (no differences in indications for section) more lacs (but less severe) preterm, Apgars, dystocia, hypertensive disorders not statistically significant.
Attrition:	No info on dropouts
Quality Score:	Fair/Good

Study 11 **KQ1**	Scott, D. A., Loveman, E., McIntyre, L., & Waugh, N. (2002) *Screening for gestational diabetes: A systematic review and economic evaluation*
Study Question:	What is the current knowledge and what are research needs to assist with policy making in the interim, pending future research?
Source of Funding:	NHS R&D Health Technology Assessment (HTA) Programme

Source Population:	All primary studies that investigated any method of screening for GDM were included. authors person reference collections, MEDLINE, EMBASE, and the Cochrane library. Citations of retrieved reference were also searched. Authors of studies reviewed were not contacted
Study Population:	Majority of studies were case series; number were quasi-experimental observational studies. No studies that evaluated the effects of antecedent diabetes, or studies that did not evaluate screening for GDM in some way. Only English language studies were identified. Unrestricted to study design.
Design:	Systematic Review
Intervention:	Tests and thresholds used for screening and diagnosis, incidence of GDM, sensitivity, specificity and positive predictive value (PPV) of the tests, country of study, time of testing and fasting status.
Intervention Setting:	National Institute for Clinical Excellence (NICE)
Comparison:	The GTT is regarded as the 'gold standard' for diagnosis of GDM
Measurement:	Data extracted included tests and thresholds used for screening and diagnosis, incidence of GDM, sensitivity, specificity, and positive predictive value of the tests, country of study, time of testing and fasting status. Risk factor screening, urine testing, various blood tests, and combinations thereof.
Results:	Different diagnostic tests and screening tests. Mostly observational studies, few incorporating control groups. Few studies have used an RCT design. Benefits reported in reduction of macrosomia not adverse outcomes. FPG values may not be relevant because postprandial values may be more closely linked with fetal weight gain. High diagnostic threshold should be used because low values are low risk. FPG <4.8 mmol/L should exclude GDM.
Attrition:	N/A
Quality Score:	Good

Study 12 **KQ1**	Seshiah, V., Balaji, V., Balaji, M. S., et al. (2007) *Glycemic level at the first visit and prediction of GDM*
Study Question:	What glycemic level at first visit is likely to predict gestational diabetes mellitus?
Source of Funding:	World Diabetes Foundation (Denmark)
Source Population:	4151 pregnant women attending the antenatal health posts across Chennai city
Study Population:	739 consecutive women with GDM were enrolled irrespective of gestational weeks. Women with pre-gestational diabetes were excluded
Design:	Prospective cohort study
Intervention:	2-hr, 75-g OGTT at first antenatal visit
Intervention Setting:	Community based study
Comparison:	2-hr, 75-g OGTT at subsequent antenatal visits
Measurement:	Diagnosis made based on WHO criteria. Value of 140 mg/dL used as diagnosis of GDM. Retrospectively looked at glycemic index at the first visit of the 211 women who manifested GDM later. 120 mg/dL used as cut-off to determine predictive value of first visit OGTT because this level maximizes sensitivity and specificity in predicting macrosomia.
Results:	2hrPG < 120 mg/dL. 56% of those who would go on to develop GDM had levels ≥ 120 mg/dL. 44% of those who would go on to develop GDM had levels < 120 mg/dL. Macrosomia occurs on a continuum with 2hrPG. Irrespective of 2hrPG (≥ or < 120) at first visit, women may still develop GDM. No first visit glycemic level predicted GDM
Attrition:	Attrition not addressed
Quality Score:	Poor

Study 13 **KQ2**	Syed, M., Javed, H., Yakoob, M. Y., & Bhutta, Z. A. (2011) *Effect of screening and management of diabetes during pregnancy on stillbirths*
Study Question:	What is the potential impact of early detection and control of diabetes mellitus during pregnancy on stillbirths?
Source of Funding:	A grant to the US Fund for UNICEF from the Bill & Melinda Gates Foundation
Source Population:	Searched PubMed, Cochrane Database, WHO Regional Databases, hand search of bibliographies. Experts contacted
Study Population:	Developed and developing countries. Included populations not described. Irrespective of language. Articles included in meta-analysis irrespective of methodological quality. Exclusion criteria: Studies that did not report on relevant outcomes. Studies that did not focus on the selected intervention. 70 studies included (14 intervention, and 56 observational)
Design:	Systematic review
Intervention:	Studies linking early screening, control, and detection of GDM and stillbirth
Intervention Setting:	The studies selected were from both developed and developing countries
Comparison:	Standard screening (glucose challenge test between 24th to 28th week of gestation
Measurement:	Meta-analysis for any outcome with more than one study. Visual inspection for statistical heterogeneity. An I2 value greater than 50% was taken to represent substantial and high heterogeneity. The CHERG adaptation of the GRADE criteria was applied to grade the evidence presented by the studies in our meta-analyses. For the intervention of diabetes screening and management, in general, during pregnancy, expert consensus was also sought via the Delphi method.
Results:	One study and one review unable to show early testing better than late in improving perinatal mortality. No difference in screening guidelines on stillbirth rates (ADA & WHO).
Attrition:	N/A

Quality Score:	Good

Study 14 **KQ1**	Zhu, W. W., Yang, H. X., Wei, Y. M., et al. (2013). *Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in china.*
Study Question:	What is the value of fasting plasma glucose value in the first prenatal visit to diagnose GDM?
Source of Funding:	NR
Source Population:	17,186 pregnant women who received care at the GDM centers at 13 different hospitals in China.
Study Population:	14,039 pregnant women with blood glucose test results linked to gestational week were available for analysis. Previously known diabetic patients were excluded
Design:	Retrospective cohort study
Intervention:	FPG at first prenatal visit
Intervention Setting:	GDM centers at 13 different hospitals in China
Comparison:	One step GDM screen (75-g) OGTT at 24-28 weeks gestation
Measurement:	FPG performed at first prenatal visit. 75-g OGTT at 24-28 week. Diagnosis according to the criteria established by MOH China.
Results:	Median first trimester FPG was 4.58 ± 0.44 mmol/L; 17.5% of patients diagnosed with GDM. Incidence of GDM increased with every 0.50 mmol/L increase in FPG. FPG values decreased throughout pregnancy. When the FPG cutoff at the first visit was 5.60 specificity was 0.99 (no sensitivity given). > 7 mmol/L considered diagnostic of previous undiagnosed diabetes. 6.10-6.99 mmol/L be treated as GDM. 5.10-6.09 mmol/L nutrition and exercise advice.
Attrition:	No attrition
Quality Score:	Fair/Good